IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
MICHITAKA SATO, et al.
Serial No. 10/590,707 Art Unit 1624
Filed: August 25, 2006 Examiner: Erich A Leeser
For: PYRIMIDINE DERIVATIVES

DECLARATION UNDER RULE 1.132

Honorable Commissioner of
Patent and Trademarks
Washington, D.C.

Sir:

I, Teruaki Matsui, hereby declare as follows:

That, in 1988, I graduated from Chiba University, and, in 1990, I completed the Course of M.S. in organic chemistry at Chiba University;

That, in the same year, I joined Teikoku Hormone Mfg. Co., Ltd. (which changed its name to ASKA Pharmaceutical Co., Ltd. on October 1, 2005), and was assigned to the Chemical Research Division;

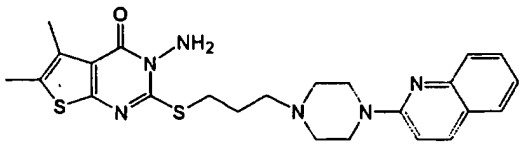
That the research field which I have mainly engaged in is the synthesis of organic compounds;

That I am one of the co-inventors of U. S. Application Serial No. 10/590,707;

That the following experiments were carried out by myself, or under my supervision and control.

[I] Synthesis of test compounds:

(1) Synthesis of 3-amino-5,6-dimethyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)-propylthio]-3H-thieno[2,3-d]pyrimidin-4-one:



(a) Synthesis of 2-piperazin-1-ylquinoline:

To a solution formed by dissolving 4.31 g of anhydrous piperazine in 30 ml of ethylene glycol, 818 mg of 2-chloroquinoline was added, and stirred at 140°C for 2 hours. After cooling, saturated aqueous sodium hydrogencarbonate solution was added, and the system was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (chloroform: methanol = 2:1) to provide 1.09 g (100%) of 2-piperazin-1-ylquinoline.

$^1$H-NMR($CDCl_3$)δ:7.89(d,J=9.2Hz,1H),7.70(d,J=8.4Hz,1H),
7.59(dd,J=1.5Hz,8.0Hz,1H), 7.53(ddd,J=1.5Hz,7.0Hz,8.4Hz,1H),
7.26~7.22(m,1H), 6.97(d,J=9.2Hz,1H),3.70(t,J=5.0Hz,4H),
3.01(t,J=5.0Hz,4H)
Mass,m/e:213($M^+$),145(base)

(b) Synthesis of 2-[4-(3-chloropropyl)piperazin-1-yl]quinoline:

Dissolving 853 mg of 2-piperazin-1-ylquinoline as prepared in above in 5 ml of acetone, 5 ml of an aqueous solution containing 160 mg of sodium hydroxide was added to the solution, and into which 0.5 ml of 1-bromo-3-chloropropane was dropped, followed by stirring for an overnight at room temperature. Then diethyl ether was added, followed by washing with saturated aqueous sodium hydrogencarbonate solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure, and the residue was purified on silica gel column chromatography (chloroform : methanol = 50:1) to provide 1.10 g

(95%) of 2-[4-(3-chloropropyl)piperazin-1-yl]quinoline.

$^1$H-NMR($CDCl_3$)δ:7.89(d,J=9.2Hz,1H),7.70(d,J=8.4Hz,1H),
7.59(dd,J=1.4Hz,8.0Hz,1H),
7.53(ddd,J=1.5Hz,7.1Hz,8.5Hz,1H),
7.22(ddd,J=1.1Hz,6.9Hz,8.0Hz,1H),6.98(d,J=9.2Hz,1H),
3.75(t,J=5.1Hz,4H),3.61(t,J=6.5Hz,2H),2.63~2.43(m,6H),
2.04~1.97(m,2H)
Mass,m/e:289($M^+$),157(base)

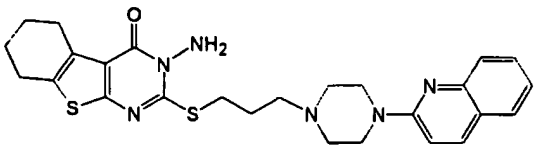
(c) Synthesis of 3-amino-5,6-dimethyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)-propylthio]-3H-thieno[2,3-d]pyrimidin-4-one:

A mixture of 80 mg of potassium 3-amino-5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-thiolate, which was prepared from ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate; 104 mg of 2-[4-(3-chloropropyl)piperazin-1-yl]quinoline as prepared in above; and 5 ml of ethanol, was heated under reflux for 4.5 hours. After cooling off the reaction mixture, chloroform was added, followed by washing with saturated brine. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified on silica gel column chromatography (chloroform : methanol = 100 : 1) to provide 72 mg (50%) of 3-amino-5,6-dimethyl-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[2,3-d]pyrimidin-4-one.

$^1$H-NMR($CDCl_3$)δ:7.89(d,J=8.7Hz,1H),7.70(d,J=8.4Hz,1H),
7.59(d,J=8.1Hz,1H),7.54~7.52(m,1H),7.23~7.20(m,1H),
6.99(d,J=9.2Hz,1H),4.77(s,2H),3.79(t,J=5.1Hz,4H),
3.19(t,J=7.3Hz,2H),2.62(t,J=5.1Hz,4H),2.56(t,J=7.0Hz,2H),
2.45(s,3H),2.36(s,3H),2.00(q,J=7.3Hz,2H)
IR(KBr)vmax:3308,2916,1668,1604,1506$cm^{-1}$
Mass,m/e:480($M^+$),157(base)

(2) Synthesis of 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)-propylthio]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]-

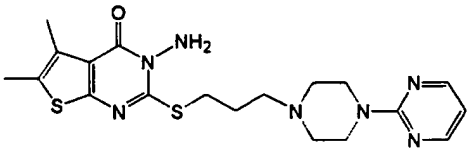
pyrimidin-4-one:



A mixture of 87 mg of potassium 3-amino-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidine-2-thiolate prepared from ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiofen-3-carboxylate, 104 mg of 2-[4-(3-chloropropyl)piperazin-1-yl]quinoline prepared in the above (1)-(b) and 3 ml of ethanol was heated under reflux for 3 hours. After cooled, the mixture was filtered, and residue was washed with a small amount of ethanol and purified water, and was then dried to give 91 mg (60 %) of 3-amino-2-[3-(4-quinolin-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one.

$^1$H-NMR($CDCl_3$)δ:7.88(d,J=8.7Hz,1H),7.70(d,J=7.8Hz,1H),
7.59(dd,J=1.3Hz,8.0Hz,1H),7.53(m,1H),7.24~7.20(m,1H),
6.99(d,J=9.2Hz,1H),4.77(s,2H),3.79(t,J=5.1Hz,4H),
3.21~3.17(m,2H),2.99~2.95(m,2H),2.75~2.71(m,2H),
2.62(t,J=5.1Hz,4H),2.56(t,J=7.0Hz,2H),1.99(q,J=7.3Hz,2H),
1.91~1.80(m,4H)
Mass,m/e:506($M^+$),157(base)

(3) Synthesis of 3-amino-5,6-dimethyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthio]-3H-thieno-[2,3-d]pyrimidin-4-one:



(a) Synthesis of 2-[4-(3-chloropropyl)piperazin-1-yl]pyrimidine:

In 12 ml of acetone, 2.37 g of 2-piperazin-1-ylpyrimidine hydrochloride was dissolved, and, to the resultant solution, 5 ml of aqueous solution of 1.20 g of sodium hydroxide was added, and, furthermore, 1.1 ml of 1-bromo-3-chloropropane was added dropwise. The resultant mixture was stirred at room temperature for 15 hours. Subsequently, diethyl ether

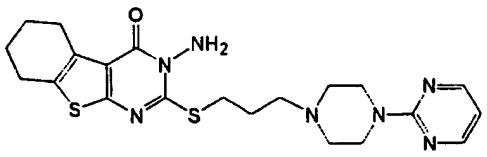
was added, and the resultant mixture was washed with saturated aqueous solution of sodium hydrogencarbonate. Organic layer was dried with anhydrous magnesium sulfate, and, then, solvent was distilled off under reduced pressure. Residue was purified with silica gel column chromatography (chloroform : methanol = 50 : 1 → 20 : 1), and, thus, 2.33 g (97 %) of 2-[4-(3-chloropropyl)piperazin-1-yl]pyrimidine was obtained.

(b) Synthesis of 3-amino-5,6-dimethyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[2,3-d]pyrimidin-4-one:

A mixture of 159 mg of potassium 3-amino-5,6-dimethyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-thiolate prepared from ethyl 2-amino-4,5-dimethylthiofen-3-carboxylate, 173 mg of 2-[4-(3-chloropropyl)-piperazin-1-yl]pyrimidine prepared in the above (3)-(a) and 3 ml of ethanol was heated under reflux for 4.5 hours. After cooled, the mixture was filtered, and residue was washed with a small amount of ethanol and purified water, and was then dried to give 144 mg (56 %) of 3-amino-5,6-dimethyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthio]-3H-thieno-[2,3-d]pyrimidin-4-one.

$^1$H-NMR($CDCl_3$)δ:8.31(d,J=4.6Hz,2H),6.48(dd,J=4.7Hz,4.7Hz,1H), 4.77(s,2H),3.86(t,J=4.7Hz,4H),3.18(t,J=7.1Hz,2H),2.55~2.52(m,6H), 2.44(d,J=0.5Hz,3H),2.36(d,J=0.5Hz,3H),2.01~1.94(m,2H)
Mass,m/e:431($M^+$),84(base)

(4) Synthesis of 3-amino-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one:

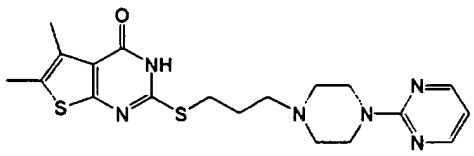



A mixture of 175 mg of potassium 3-amino-4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidine-2-thiolate prepared from ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiofen-3-carboxylate, 173 mg of 2-[4-(3-chloropropyl)piperazin-1-yl]pyrimidine prepared in the above (3)-(a)

and 3 ml of ethanol was heated under reflux for 14 hours. After cooled, the mixture was filtered, and residue was washed with a small amount of ethanol and purified water, and was then dried to give 97 mg (35 %) of 3-amino-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one.

$^1$H-NMR($CDCl_3$)δ:8.31(d,J=4.8Hz,2H),6.48(dd,J=4.8Hz,4.8Hz,1H), 4.77(s,2H),3.85(t,J=5.0Hz,4H),3.21~3.16(m,2H),2.98~2.95(m,2H), 2.76~2.73(m,2H),2.55~2.52(m,6H),2.01~1.94(m,2H),1.91~1.81(m,4H)
Mass,m/e:457($M^+$),84(base)

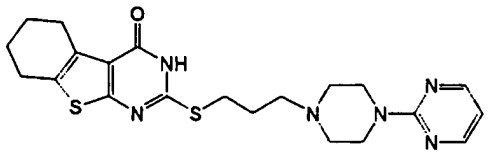
(5) Synthesis of 5,6-dimethyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)-propylthio]-3H-thieno[2,3-d]pyrimidin-4-one:



A mixture of 75 mg of potassium 5,6-dimethyl-4-oxo-3,4-dihydro thieno[2,3-d]pyrimidine-2-thiolate prepared from ethyl 2-amino-4,5-dimethylthiofen-3-carboxylate, 86 mg of 2-[4-(3-chloropropyl)piperazin-1-yl]pyrimidine prepared in the above (3)-(a) and 3 ml of ethanol was heated under reflux for 6 hours. After cooling, solvent was distilled off under reduced pressure. Residue was purified with silica gel column chromatography (chloroform : methanol = 100 : 1 → 25 : 1), and, thus, 112 mg (90 %) of 5,6-dimethyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propyl-thio]-3H-thieno[2,3-d]pyrimidin-4-one was obtained.

$^1$H-NMR($CDCl_3$)δ:8.30(d,J=4.7Hz,2H),6.48(dd,J=4.7Hz,4.7Hz,1H), 3.95~3.92(m,4H),3.29(t,J=6.9Hz,2H),2.61~2.56(m,6H), 2.43(d,J=0.7Hz,3H),2.35(d,J=0.7Hz,3H),2.03~1.98(m,2H)
Mass,m/e:416($M^+$),96(base)

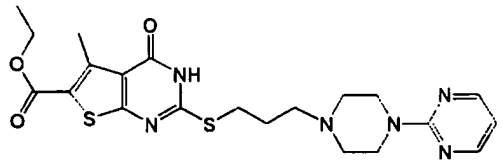
(6) Synthesis of 2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthio]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one:



A mixture of 83 mg of potassium 4-oxo-3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-d]pyrimidine-2-thiolate prepared from ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiofen-3-carboxylate, 86 mg of 2-[4-(3-chloropropyl)piperazin-1-yl]pyrimidine prepared in the above (3)-(a) and 3 ml of ethanol was heated under reflux for 6 hours. After cooling, solvent was distilled off under reduced pressure. Residue was purified with silica gel column chromatography (chloroform : methanol = 100 : 1 → 25 : 1), and, thus, 106 mg (80 %) of 2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)-propylthio]-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-d]pyrimidin-4-one was obtained.

$^1$H-NMR($CDCl_3$)δ:8.30(d,J=4.8Hz,2H),6.47(dd,J=4.8Hz,4.8Hz,1H),
3.95(t,J=5.0Hz,4H),3.29(t,J=6.9Hz,2H),2.95(t,J=6.0Hz,2H),
2.73(t,J=6.0Hz,2H),2.61~2.55(m,6H),2.02~1.96(m,2H),
1.90~1.79(m,4H)
Mass,m/e:442($M^+$),96(base)

(7) Synthesis of ethyl 5-methyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)-propylthio]-3H-thieno[2,3-d]pyrimidin-4-one-6-carboxylate:

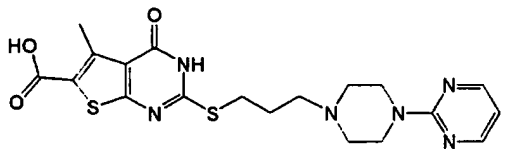


A mixture of 96 mg of potassium 6-ethoxycarbonyl-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-2-thiolate prepared from diethyl 5-amino-3-methylthiofen-2,4-dicarboxylate, 86 mg of 2-[4-(3-chloropropyl)-piperazin-1-yl]pyrimidine prepared in the above (3)-(a) and 3 ml of ethanol was heated under reflux for 4 hours. After cooling, solvent was distilled off

under reduced pressure. Residue was purified with silica gel column chromatography (chloroform : methanol = 100 : 1 → 25 : 1), and, thus, 93 mg (65 %) of ethyl 5-methyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propyl-thio]-3H-thieno[2,3-d]-pyrimidin-4-one-6-carboxylate was obtained.

$^1$H-NMR($CDCl_3$)δ:8.30(d,J=4.8Hz,2H),6.48(dd,J=4.8Hz,4.8Hz,1H),
4.35(q,J=7.1Hz,2H),3.94~3.91(m,4H),3.29~3.26(m,2H),2.86(s,3H),
2.67~2.64(m,6H),2.09~2.05(m,2H),1.39(t,J=7.1Hz,3H)
Mass,m/e:474($M^+$),108(base)

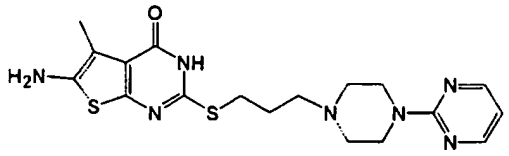
(8) Synthesis of 5-methyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[2,3-d]pyrimidin-4-one-6-carboxylic acid:




There was added 104 mg of ethyl 5-methyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[2,3-d]pyrimidin-4-one-6-carboxylate as prepared in the above (7) to a mixed solution of 0.24 ml of 1N aqueous solution of sodium hydroxide and 1.8 ml of purified water, and the resultant mixture was stirred at 70°C for 3 hours. After cooled, the mixture was neutralized with 2N hydrochloric acid, and precipitate was filtered out. The precipitate was then purified with a small amount of purified water, and was dried to give 82 mg (84 %) of 5-methyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[2,3-d]pyrimidin-4-one-6-carboxylic acid.

$^1$H-NMR(DMSO-$d_6$)δ:8.34(d,J=4.7Hz,2H),
6.60(dd,J=4.7Hz,4.7Hz,1H),3.77~3.74(m,4H),3.23(t,J=7.2Hz,2H),
2.76(s,3H),2.50~2.44(m,6H),1.90~1.86(m,2H)
Mass,m/e:446($M^+$),108(base)

(9) Synthesis of 6-amino-5-methyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)-propylthio]-3H-thieno-[2,3-d]pyrimidin-4-one:



There was dissolved 40 mg of 5-methyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)propylthio]-3H-thieno[2,3-d]pyrimidin-4-one-6-carboxylic acid as prepared in the above (8) in 4 ml of tert-butanol, and, to the resultant solution, 9 mg of triethyl amine was added under ice cooling. After 26 mg of DPPA was added, the resultant mixture was heated under reflux for 5 hours. After cooling, solvent was distilled off under reduced pressure. Residue was purified with silica gel column chromatography (chloroform : methanol = 50 : 1), and was then added to 4 ml of 15 % of hydrochloric acid-methanol solution. After stirring for 1.5 hours, triethyl amine was added for neutralization. The resultant solution was concentraed under reduced pressure. Residue was purified with silica gel column chromatography (chloroform : methanol = 50 : 1 → 20 : 1) to give 10 mg (41 %) of 6-amino-5-methyl-2-[3-(4-pyrimidin-2-ylpiperazin-1-yl)-propylthio]-3H-thieno[2,3-d]pyrimidin-4-one.

$^1$H-NMR($CDCl_3$)δ:8.31(d,J=4.8Hz,2H),6.48(dd,J=4.8Hz,4.8Hz,1H),
4.01~3.93(m,4H),3.61(br s,2H),3.26(t,J=6.8Hz,2H),2.68~2.58(m,6H),
2.34(s,3H),2.04~1.99(m,2H)
Mass,m/e:417(M+),96(base)

[II] Affinity measurement:

(1) Measurement of affinity of the compounds to human 5-$HT_{1A}$ receptor (in vitro):

CHO cell membrane sample in which human 5-$HT_{1A}$ receptor was expressed (purchased from Packard Bioscience) in an amount of 0.25 mL (about 50 units) was added to 24.75 mL of incubation buffer solution A (an aqueous solution of a mixture of 50 mmols/L of Tris-hydrochloric acid, 10

mmols/L of magnesium sulfate, 0.5 mmols/L of EDTA and 0.1% ascorbic acid, whose pH was adjusted to 7.4 at 27°C with 1N-aqueous sodium hydroxide solution), and labeled as membrane sample suspension A. Separately, each test compound was made into 270 μmols/L DMSO solution and diluted to a prescribed concentration with the incubation buffer solution A, to provide a compound solution.

A piece of polypropylene tube was charged with 20 μL of [3H]8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetralin; purchased from Daiichi Pure Chemicals Co., Ltd.) (The concentration of the [3H]8-OH-DPAT had in advance been adjusted to render its concentration in the reaction mixture to 0.25 nmols/L) and 20 μL of one of the compound solutions. Further 500 μL of the membrane sample suspension A was added into the tube, followed by 60 minutes' incubation at 27°C. The reaction was terminated by rapid filtration of the reaction mixture through GF/C filter which had in advance been immersed in a solution formed by adding to the incubation buffer solution A polyethyleneimine to a concentration of 0.3%, using Brandel cell harvester. Then the filter was washed with about 5 mL of 50 mmols/L of Tris-hydrochloric acid which had been cooled to 4°C. The filter was once again washed after similar operation.

Residual radioactivity on the filter was measured with liquid scintillation counter (Aloka Co., LSC-5100). Percent inhibition (%) of each test compound to binding of [3H]8-OH-DPAT to 5-$HT_{1A}$ receptor at a concentration of 0.25 nmols/L, i.e., affinity of each test compound to 5-$HT_{1A}$ receptor, can be calculated according to the following expression. The ratio of non-specific binding was calculated by measuring the radioactivity in case of using 8-OH-DPAT at a concentration of 10 μmols/L, with which value the measured value of each test compound was compensated.

$$\left[ 1 - \frac{\text{radioactivity when each test compound was used}}{\text{radioactivity in the control experiment}} \times 100 \right]$$

(2) Measurement of affinity of the compounds to human 5-$HT_3$ receptor (in vitro):

HEK-293 cell membrane sample in which human 5-$HT_3$ receptor was expressed (purchased from BIOLINKS K.K.) in an amount of 0.05 mL (about 50 microassay) was added to 24.95 mL of incubation buffer solution B (an aqueous solution of a mixture of 50 mmols/L of Tris-hydrochloric acid, 5 mmols/L of magnesium chloride and 1 mmol/L of EDTA, whose pH was adjusted to 7.5 at 25°C with 1N-aqueous sodium hydroxide solution) and homogenized, to provide a membrane sample suspension B. Separately, each test compound was made into 270 μmols/L of DMSO solution and diluted to a prescribed concentration with the incubation buffer solution B to provide a compound solution.

A piece of polypropylene tube was charged with 20 μL of [3H]BRL-43694 (purchased from Daiichi Pure Chemicals Co., Ltd.) (The concentration of [3H]BRL-43694 had in advance been adjusted to render its concentration in the reaction mixture to 0.5 nmols/L.) and 20 μL of one of the compound solutions. Further 500 μL of the membrane sample suspension B was added into the tube, followed by 60 minutes' incubation at 25°C. The reaction was terminated by rapid filtration of the reaction mixture through GF/B filter which had in advance been immersed in a solution formed by adding to the incubation buffer solution B polyethyleneimine to a concentration of 0.5%, using Brandel cell harvester. Then the filter was washed with about 5 mL of 50 mmols/L of Tris-hydrochloric acid which had been cooled to 4°C. The filter was once again washed after similar operation.

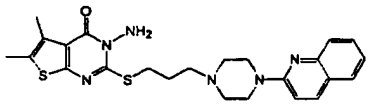
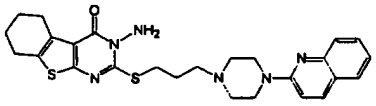
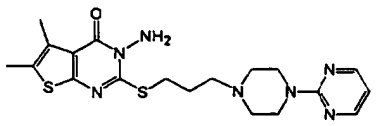
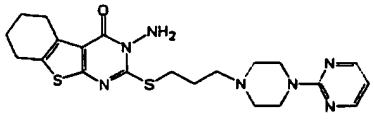
Residual radioactivity on the filter was measured with liquid scintillation counter (ALOKA CO., LTD. LSC-5100). Percent inhibition (%) of each test compound to binding of [3H]BRL-43694 to 5-HT3 receptor at a concentration of 0.5 nmols/L, i.e., affinity of each test compound to 5-HT3 receptor, can be calculated according to the following expression. The ratio of non-specific binding was calculated by measuring the radioactivity in case of using tropisetron: (ICS 205-930) at a concentration of 10 μmols/L, with which value the measured value of each test compound was compensated.

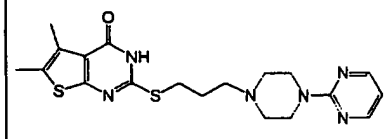
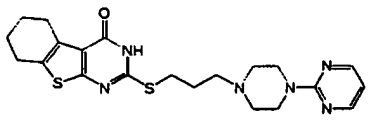
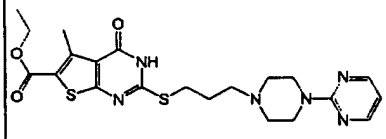
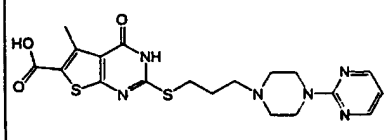
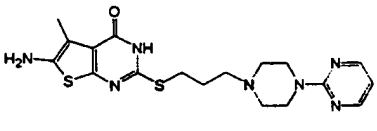
$$\left[\ 1 - \frac{\text{radioactivity when each test compound was used}}{\text{radioactivity in the control experiment}} \times 100\ \right]$$

[III] Result:

Affinity of the compounds to 5-$HT_{1A}$ receptor and 5-$HT_3$ receptor are shown in Table 1.

Table 1

| Compound | Structure | 5-$HT_{1A}$ inhibit(%) | | | 5-$HT_3$ inhibit(%) | | |
|---|---|---|---|---|---|---|---|
| | | $10^{-6}$M | $10^{-7}$M | $10^{-8}$M | $10^{-6}$M | $10^{-7}$M | $10^{-8}$M |
| a compound of Example 1-1 in present application |  | 99.7 | 94.5 | 31.5 | 99.9 | 94.0 | 17.2 |
| a compound of Example 1-4 in present application |  | 99.8 | 96.6 | 51.3 | 100.2 | 93.2 | 26.8 |
| a compound synthesized in [I]-(3) |  | 98.7 | 97.8 | 68.1 | 35.0 | ND | ND |
| a compound synthesized in [I]-(4) |  | 84.2 | 96.3 | 65.6 | 12.6 | ND | ND |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| a compound synthesized in [I]-(5) |  | 90.6 | ND | ND | 89.6 | 19.3 | ND |
| a compound synthesized in [I]-(6) |  | 89.0 | ND | ND | 45.9 | ND | ND |
| a compound synthesized in [I]-(7) |  | 85.2 | ND | ND | 52.7 | -3.8 | ND |
| a compound synthesized in [I]-(8) |  | 55.0 | ND | ND | 3.0 | ND | ND |
| a compound synthesized in [I]-(9) |  | 90.4 | 43.2 | ND | 57.6 | ND | ND |

ND:No Data

The undersigned declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Signed this 27 day of February, 2008

Teruaki Matsui

Teruaki Matsui